REMARKS

Favorable reconsideration of this application, in light of the preceding amendments and following remarks, is respectfully requested.

Claims 8-23 are pending in this application. Claims 8-9, 13-14, 17 and 20 are amended and claims 1-7 have been cancelled. Claims 8, 14 and 17 are the independent claims.

Applicants note with appreciation the Examiner's acknowledgement that certified copies of all priority documents have been received by the U.S.P.T.O. Action, summary at 12.

Applicants also respectfully note that the present action does not indicate that the drawings have been accepted by the Examiner. Applicants respectfully request that the Examiner's next communication include an indication as to the acceptability of the filed drawings or as to any perceived deficiencies so that the Applicants may have a full and fair opportunity to submit appropriate amendments and/or corrections to the drawings.

Claim Objections

Claim 20 has been objected to because of informalities. Applicants have corrected the minor typographical error in claim 20, and therefore, withdrawal of the objection to claim 20 is respectfully requested.

Rejections under 35 U.S.C. § 101

Claims 1-7 stand rejected under 35 U.S.C. § 101 because the claimed recitation of a use, without setting forth any steps involved in the process,

results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. Claims 1-7 have been cancelled, and therefore, the rejection of claims 1-7 is now moot. The Applicants, therefore, respectfully request that the rejection to Claims 1-7 under 35 U.S.C. § 101 be withdrawn.

Rejections under 35 U.S.C. § 112

A. Second Paragraph

a. Claims 1-7

Claims 1-7 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 1-7 have been cancelled, and therefore, the rejection of claims 1-7 is now moot. The Applicants, therefore, respectfully request that the rejection to Claims 1-7 under 35 U.S.C. § 112 be withdrawn.

b. Claims 1-23

Claims 1-23 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 1-7 have been cancelled, and therefore, the rejection of claims 1-7 is now moot. Applicants have amended independent claims 8, 9, 14 and 17 for clarification in accordance with the Examiner's comments. The Applicants, therefore, respectfully request that the rejection to Claims 1-23 under 35 U.S.C. § 112 be withdrawn.

c. Claims 2 and 9

Claims 2 and 9 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection for the reasons detailed below.

Claim 2 has been cancelled, and therefore, the rejection of claim 2 is now moot. Applicants have amended claim 9 to include the full meaning of the abbreviated term "THF" in accordance with the Examiner's comments. Furthermore, Applicants respectfully submit that there is clearly sufficient antecedent basis for "said THF, methyl-THF and/or methylene-THF" in independent claim 8. The Applicants, therefore, respectfully request that the rejection to claims 2 and 9 under 35 U.S.C. § 112 be withdrawn.

d. Claims 6 and 13

Claims 6 and 13 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection for the reasons detailed below.

Claim 6 has been cancelled, and therefore, the rejection of claim 6 is now moot. Applicants have amended claim 13 for clarification in accordance with the Examiner's comments. The Applicants, therefore, respectfully request that the rejection to claims 6 and 13 under 35 U.S.C. § 112 be withdrawn.

B. First Paragraph

a. Claims 1, 2, 4-9, 11-18 and 20-23

Claims 1, 2, 4-9, 11-18 and 20-23 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection for the reasons detailed below.

The Office Action stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention; that the specification discloses that multi-targeting antifolates may be selected from the group consisting of premetrexed [sic - pemetrexed], raltitrexed, and lometrexol (page 4, lines 2830; page 15, lines 3-6As), and as such, based on Applicant's disclosure, one skilled in the art would not know what compounds, other than pemetrexed, raltitrexed, and lometrexol, are multi-targeting antifolates as recited in the instant claims.

Claims 1-2 and 4-7 have been cancelled, and therefore, the rejection of claims 1-2 and 4-7 is now moot. Applicants have amended claims 8, 14 and 17 for clarification in accordance with the Examiner's comments. The Applicants, therefore, respectfully request that the rejection to Claims 1, 2, 4-9, 11-18 and 20-23 under 35 U.S.C. § 112, first paragraph, be withdrawn.

b. Claims 17-23

Claims 17-23 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the treatment of cancer to the extent that "treatment" refers to alleviating the symptoms of cancer, does

not reasonably provide enablement for the treatment of cancer to the extent that "treatment" refers to a cure or prevention of cancer. Applicants respectfully traverse this rejection for the reasons detailed below.

Applicants have amended claim 17 for clarification in accordance with the Examiner's comments. Support for the amendment can be found at least on page 15, lines 20-25. The Applicants, therefore, respectfully request that the rejection to Claims 17-23 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 103

WO'660 in view of Hanauske and Niyikiza

Claims 1-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 91/17660 in view of The Oncologist, vol. 6, pp. 363-373 (2001) by Hanauske et al. (hereinafter "Hanauske"), in view of Molecular Cancer Therapeutics, Vol. 1, pp. 545-552 (May 2002) by Niyikiza et al. (hereinafter "Niyikiza"). Applicants respectfully traverse this rejection for the reasons detailed below.

Claims 1-7 have been cancelled, and therefore, the rejection of claims 1-7 is now moot.

Hanauske discloses that 5,10-methylene-tetrahydrofolate and tetrahydrofolate may be used in a method to reduce the toxicity of an anti-folate drug which has been administered to a patient. The anti-folate drugs disclosed are methotrexate, trimetrexate, nitrous oxide and dideoxytetrahydrofolic acid, all of which belong to the group of single enzyme

targeting antifolates. As acknowledged by the Examiner on page 14, second paragraph of the Office Action, Hanauske does **not** disclose combining methylene-tetrahydrofolate or tetrahydrofolate with **a multi-targeting antifolate selected from the group consisting of pemetrexed, raltitrexed and lometrexol,** and therefore, the Examiner relies on the teachings of Niyikiza for this feature of independent claims 8, 14 and 17.

Hanauske and Niyikiza disclose the use of folic acid supplementation to reduce the toxicity of pemetrexed (a multi-functional antifolate). Applicants are attaching evidence (FIGS. 1-6) illustrating a comparison, in terms of efficiency and toxicity in alleviating the symptoms of cancer when using a combination of pemetrexed and metylene-tetrahydrofolate as in the independent claims and a combination of pemetrexed with folic acid as taught by the cited art.

The experimental study was performed on a test system as described in Example 2 in the application with the following differences:

- The administration of pemetrexed amounted to 1.0 mg/kg and 2.0 mg/kg, respectively.
- Test groups of rats receiving pemetrexed in combination with folic acid have been added.
- The number of rats in each group was as follows:
    - 1.0 mg/kg pemetrexed + 15 mg/kg MTHF: four rats
    - 1.0 mg/kg pemetrexed + ~500 µg/day folic acid: five rats
    - 2.0 mg/kg pemetrexed + 15 mg/kg MTHF: six rats
    - 2.0 mg/kg pemetrexed + ~500 µg/day folic acid: six rats

- The body weights were recorded at day 0 and at the end of the study.

The folic acid intake was about 500 μg/day, which is a level normally employed when using folic acid with the aim of reducing toxicity (see e.g. Niyikiza, page 551, left column, penultimate paragraph). The results of the experimental study are presented, as mean values for each test group, in the enclosed FIGS. 1-6. FIGS. 1-3 show the results for the rats receiving 1.0 mg/k pemetrexed in combination with MTHF and folic acid, respectively, and FIGS. 4-6 show the results for the rats receiving 2.0 mg/kg pemetrexed in combination with MTHF and folic acid, respectively.

In FIG. 1, the rats receiving 1.0 mg/kg pemetrexed in combination with MTHF showed less weight loss as compared to the rats receiving 1.0 mg/kg pemetrexed in combination with folic acid. The same result was found for the groups receiving the higher pemetrexed dose of 2.0 mg/kg, see FIG. 4. Also, in FIGS. 2 and 5, for both doses, the tumor growth in the rats receiving pemetrexed in combination with MTHF was less than the tumor growth in rats receiving pemetrexed in combination with folic acid. Finally, the spleen weight in the rats receiving pemetrexed in combination with MTHF was higher than the spleen weight in rats receiving pemetrexed in combination with folic acid, see FIGS. 3 and 6. Applicants submit that the spleen weight is a well-known surrogate marker for toxicity and a lower spleen weight is a sing of toxicity.

As is clear from the attached evidence, combining at least one of tetrahydrofolate, methylene-tetrahydrofolate, and methyl-tetrahydrofolate, and at least one multi-targeting antifolate selected from the group consisting of

pemetrexed, raltitrexed and lometrexol as recited in independent claims 8, 14 and 17 is critical and achieves unexpected results relative to the compositions as taught by Hanauske and Niyikiza. In particular, the combination of at least one of tetrahydrofolate, methylene-tetrahydrofolate, and methyl-tetrahydrofolate, and at least one multi-targeting antifolate selected from the group consisting of pemetrexed, raltitrexed and lometrexol is not only less toxic, but also more efficient at reducing side effects and increasing anti-tumoral action than the compositions taught by Hanauske and Niykiza.

The Applicants, therefore, respectfully request that the rejection to Claims 8, 14 and 17 under 35 U.S.C. § 103(a) be withdrawn.

Claims 9-13, 15, 16 and 18-23, dependent on independent claims 8, 14 and 17, are patentable for the reasons stated above with respect to claims 8, 14 and 17 as well as for their own merits.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection to independent claims 8, 14 and 17 and all claims dependent thereon.

CONCLUSION

In view of the above remarks and amendments, the Applicants respectfully submit that each of the pending objections and rejections has been addressed and overcome, placing the present application in condition for allowance. A notice to that effect is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to contact the undersigned.

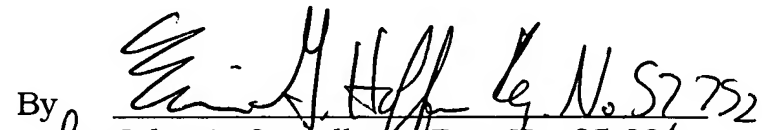
Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants hereby petition for a two (2) month extension of time for filing a reply to the outstanding Office Action and submit the required $490.00 extension fee herewith.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Erin G. Hoffman, Reg. No. 57,752, at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 08-0750 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

HARNESS, DICKEY, & PIERCE, P.L.C.

By 
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